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Dose Accuracy Testing of the Humalog®/ Humulin® Insulin Pen Device

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ABSTRACT

The primary purpose of the study was to determine whether pen users would challenge the insufficient remaining dose (IRD) stop mechanism with sufficient force to affect the dose accuracy of the final dose. The secondary purpose was to determine the participant's positive and negative impressions of the Humalog®/Humulin® pen and the likelihood of using the new prefilled pen. Three different modifications to the prefilled pen's IRD stop feature were made. These three pen models then underwent environmental dose accuracy testing at various temperatures and humidities, and user dose accuracy testing by 64 patients with diabetes. Evaluation also involved challenging the IRD stop at various dialing torques. Thirty pens from each model were tested to failure of the IRD stop. A model of the prefilled pen was selected for commercialization that met the dose accuracy targets of ± 1 unit (U) for insulin doses less than 20 U and ± 5% of dose volume for doses equal to or over 20 U. The selected pen model was superior at the minimum (1 unit), median (30 unit) and maximum (60 unit) dose volumes. Also 92% (n = 59) of patients interviewed felt that the stop mechanism for the final dose was clear. Extensive testing in the development of a prefilled insulin delivery device demonstrates an accurate and reliable medical device.

INTRODUCTION

When developing new drugs, clinical trials are conducted to provide information on safety and efficacy in order to obtain regulatory approval. In general, an insulin injector must be able to comply with global regulatory standards as well as U.S. Food and Drug Administration (FDA) regulations when these devices are manufactured and distributed in the United States. In addition, all types of insulin delivery devices developed for distribution in Europe must comply with the International Organization of Standards (ISO). These standards are a series of laboratory-based tests that confirm the device will deliver an appropriate dose over a variety of environmental conditions, for example, after being dropped from one meter in a variety of positions. The ISO regulations contain specific requirements regarding dose accuracy. The testing in this article specifically addresses the dose accuracy requirements specified in the ISO guidance document. For medical devices such as the insulin injector pens, there are no requirements to perform clinical trials in order to obtain European regulatory approval, termed the Conformity European (CE) mark. However, the CE mark requires that the pen incorporate a number of safety features to ensure accurate dosage.

The Humalog®/Humulin® Disposable Insulin Injection pen was developed by Eli Lilly

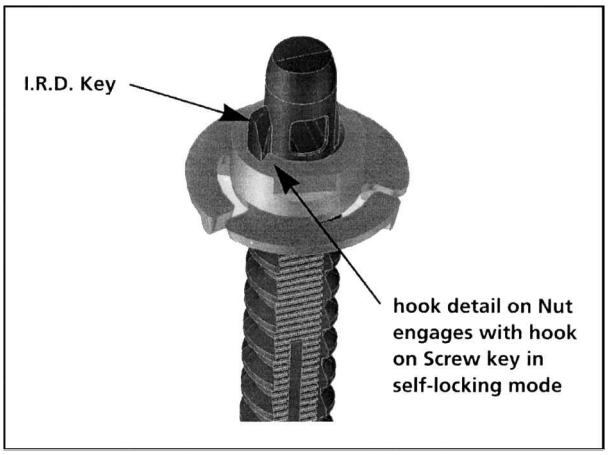


FIG. 1. "Hook and Key" IRD stop.

and Company (Indianapolis, IN) and first marketed in Europe in 1998. It is capable of administering Humalog®/Humulin® subcutaneously in accurate doses from 1 to 60 units, in 1-unit increments. At the time, it was the only insulin pen on the market that allowed for single-unit dose adjustment. The injector is designed to meet the current draft of ISO standards[1] (ISO/DIS 11608-1, 11608-2, 11608-3 TC 84) governing design verification of pen injectors for medical use.

In the pen's development, it was important to establish that all doses delivered would have the same degree of accuracy when used by patients. This created a challenge for Lilly's mechanical/design engineers. The result was a prefilled pen that contains an insufficient remaining dose (IRD) stop, which prevents the user from setting a dose greater than that remaining in the cartridge. This is done by means of a hook and key detail on the nut and screw, respectively. When the nut reaches the end of the screw, a stop in the nut threads (hook) hits a stop at the end of the screw threads (key), thus preventing the user from dialing a dose greater than the amount remaining in the cartridge (Fig. 1). When this feature is engaged, the screw is prevented from turning by the anti-backup device (ABD) fingers, which are molded into the body halves (Fig. 2).

In order for the IRD stop feature to function properly, the hook and key feature must be positioned such that the user feels an increase in dialing stiffness (the stop). This increase in stiffness should occur as the last true remaining dose starts to appear in the dose window. This indicates to the user that the number appearing in the window is the last remaining dose, and signals him or her to stop turning the dial. In addition to the above, the IRD stop should be able to withstand the maximum dialing torque expected to be exerted by users while still delivering an accurate dose; otherwise, the user could exert enough force to override the stop feature, causing an underdosing of insulin on the final dose.

This document will summarize a study of some of the torque and dose accuracy tests involved in the development of the Humalog®/Humulin® Disposable Insulin Injection pen, along with the criteria used for selection of the appropriate model for launch—that is, production and distribution to health care providers and patients with diabetes. The primary purpose of the study was to determine whether pen users would challenge the IRD stop mechanism with sufficient force to affect the dose accuracy of the final dose. And the secondary purpose was to determine the participant's positive and negative impressions of the Humalog®/Humulin® pen and the likelihood of using the new prefilled pen.

MATERIALS AND METHODS

In order to evaluate the IRD stop feature and the IRD stop strength, three different modifi-

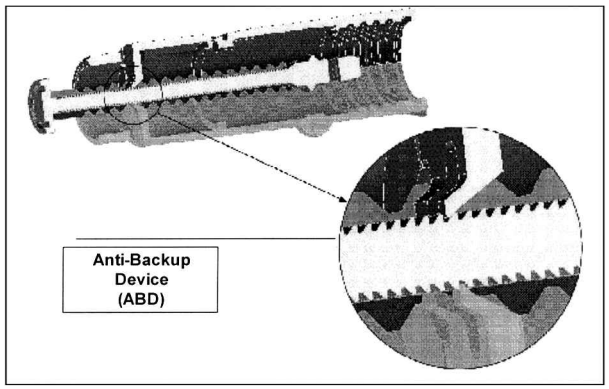


FIG. 2. ABD detail

cations to the feature in question were evaluated and then tested by actual patients with diabetes. These pen modifications will be considered prototypes Pen1, Pen2, and Pen3. The modifications made were different phasings of the nut feature—that is, the position of the hook and key feature relative to the dial interface.

Pens

The Humalog®/Humulin® Disposable Insulin Injection pen contains 3.0-mL cartridges that hold at least 300 units of Humalog®/Humulin® or other insulin mixtures, and the pen is disposed of when expended. The maximum dose possible with this pen is 60 Units (U), or 0.6 mL, and the smallest dose possible is 1 U, or 0.01 mL.

Patients

Sixty-four patients with diabetes who were currently taking insulin injections participated in the study. They completed questionnaires that contained both open-ended and closed-ended questions on new pen models and were also interviewed one-on-one at the end of the protocol exercises. The study was conducted in Columbus, Ohio, on April 8, 1998. Participants did not know that Lilly was sponsoring the study or that the Humalog®/Humulin® prefilled pen was a Lilly product.

Insufficient remaining dose accuracy

Pens were tested for IRD dose accuracy by challenging the IRD stop at various torques, reading the indicated dose, and then expelling the dose into a measuring device. From the weight and the specific gravity of the fluid, the exact volume expelled could be determined. At least 15 pens were tested at each torque. The challenge torque values were selected based on the specification for overall strength of the feature and evaluation of actual user test data.

The graph in Figure 3 shows the results of the dose accuracy testing. The horizontal axis contains the challenge torque applied in inch-ounces, while the vertical axis contains the average dose error expressed as a percentage of the indicated dose.

User test insufficient remaining dose accuracy

In this test, each individual was given one each of the three pen models, as well as a practice pen to familiarize the individual with the device. The three different pens were tested using a Graeco-Latin square design. This design allowed for randomization of the pen type as well as randomization of the dialing protocol sequence used. Dose sizes of 12, 18, 28, and 41 units were chosen in order to evaluate the feature under typical user conditions. Dose sequences were selected so that equal numbers of pens would hit the IRD stop at approximately the four chosen doses. The user did not know when the IRD stop would be reached and so would adequately challenge the stop. Twenty-five actual uses at each unique dose were measured and the accuracy of the last dose was compared to the previous 24 doses. The results of this testing are included in Figure 4.

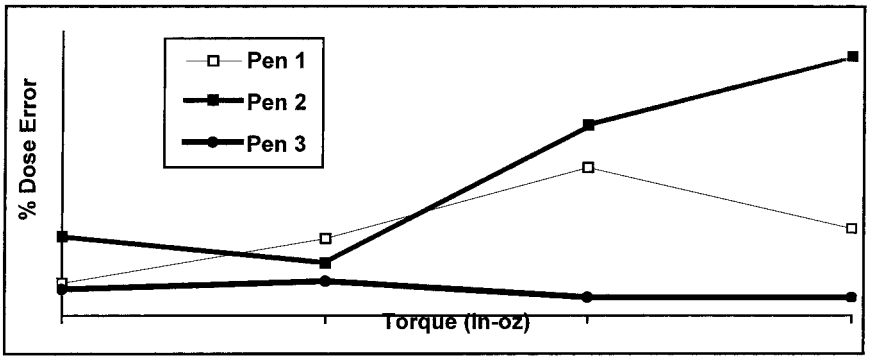


FIG. 3 Percent dose error versus patient challenge torque.

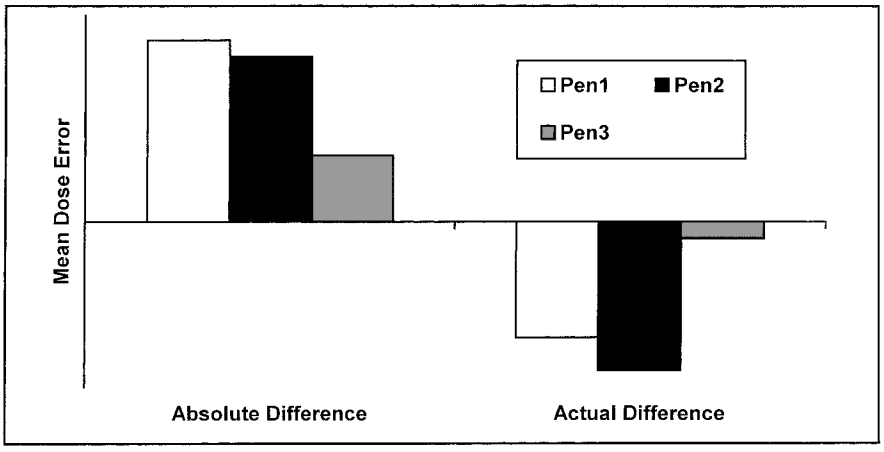


FIG. 4. Patient dose accuracy tests on three different pen models.

Insufficient remaining dose stop strength

Thirty pens from each build were tested to failure of the IRD stop, with the results detailed in the graph in Figure 5.

Level 1 and insufficient remaining dose accuracy simulation

To simulate the performance of each configuration in real-world use, the user test dose accuracy data for Pens 1, 2, and 3 were combined with what is termed level 1 dose accuracy data for control pens. That is, dose events at the IRD stop were combined with a group of level 1 dose accuracy data.

In order to determine how many IRD doses to include at each dose size, the following formula was used:

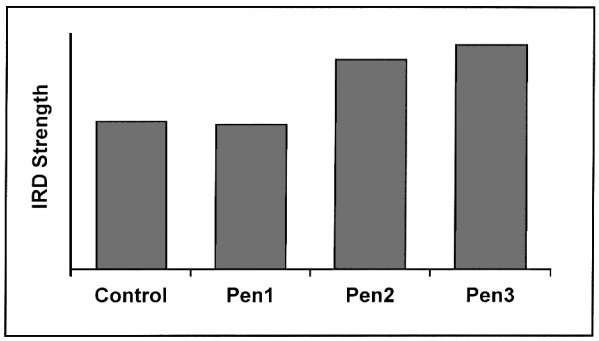
30-unit dose: [(30 units/dose) × (60 doses/test)]/(300 units/pen) = 6 pens per test

In the example above, one would expect six pens to be used in the test. At the end of each pen test, the IRD feature would be engaged, so six IRD doses are included at the 30-unit level.

60-unit dose: [(60 units/dose) × (60 doses/test)]/(300 units/pen) = 12 pens per test

The IRD doses were combined with actual level 1 test data from a control model build. For ture [cool (5°C), standard (23°C with 50% relative humidity), and hot (40°C with 50% relative humidity)], 1,000 trials were run in a simulation program and the resulting K values (tolerance limit factors) were recorded. The results are expressed as the probability of obtaining a K value higher than the required target K value. The target K value varied slightly for each group due to the different number of IRD doses included at each dose size.

These results are summarized in Figure 6. In each instance, a probability of less than 100% means that the IRD doses have an adverse impact on the likelihood of the prefilled pen passing dose accuracy standards. It is important to note that the representations in Figure 6 should not be confused with the confidence interval or p content of a dose accuracy test. They represent the impact that the inclusion of the IRD dose has on the overall dose accuracy of a certain body of data, with higher percentages being more desirable than lower percentages.



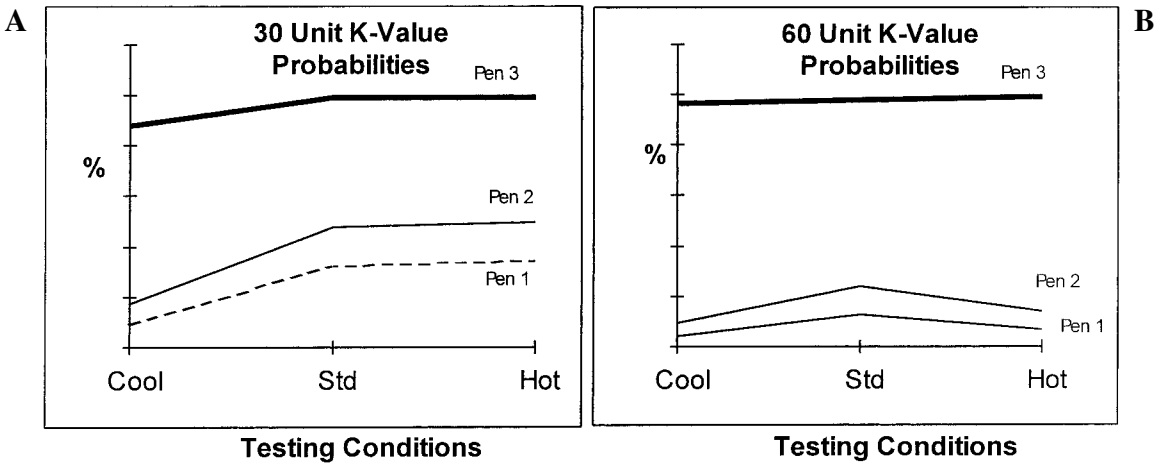


FIG. 6. 30U (**A**) and 60U (**B**) *K* value probabilities versus temperature.

RESULTS

Patients

A total of 64 patients with diabetes were involved in evaluating the three pen models (52 patients produced a complete set of three test results). There were 26 males (40%) and 38 females (60%) included in the study; all were currently using insulin injections prior to the study. The majority of patients were using a needle and syringe (88%; $n = 56$), while 6%, or $n = 4$, were using the insulin pump, and 3%, or $n = 2$, were using the pen and 3%, or $n = 2$, were using both the pen and syringe and needles. The patient's age at diagnosis was 30 or younger for 30%, $n = 19$, and over age 30 for 70%, $n = 45$.

Analysis A: binomial method

The absolute values of the differences from nominal were compared. This is the actual difference in the dose delivered by the pen versus the dose indicated by the dial on the pen at the beginning of the injection. This difference was calculated at small, medium, and large dose sizes. Each pair-wise comparison was made and tested: Pen 1 versus Pen 2, Pen 1 versus Pen 3, Pen 2 versus Pen 3. For example, in the comparison of 1 versus 2, in 32 of 58 subjects, Pen 1 delivered a dose closer to the indicated value. Pen 2 was closer to indicated value in 26 of 58 subjects. If the pens were identical, one would expect, on the average, a 29/29 breakbinomial distribution, the p value for a 32/26 breakdown is 0.5114, meaning that there is about a 50% chance of obtaining a result of 32/26 or more extreme (such as 34/24 or 26/32), given the pens are no different. Therefore, 32/26 is not strong evidence to suggest that they are different with respect to delivering doses close to indicated value.

Comparisons	*Closer to nominal*	*p value*
Pen 1 vs. Pen 2	Pen 1, 32; Pen 2, 26	0.5114
Pen 1 vs. Pen 3	Pen 1, 18; Pen 3, 38	0.0111
Pen 2 vs. Pen 3	Pen 2, 15; Pen 3, 42	0.0006

Analysis A results. Pens 1 and 2 are not significantly different at the 95% confidence level. Pen 3 is significantly better in dose delivery than Pen 1 and Pen 2.

Analysis B: nonparametric test on absolute difference from indicated dose

Again, the absolute value of the differential was calculated for each pen, each patient. The mean delta between the two pens was graphed and tested against 0 (zero). If a test shows a mean delta significantly different from 0, the deviations (from indicated) on one pen are deemed larger than deviations from the other pen. Because a couple of the deltas were far askew from the other data points, the distributions in two of the three cases were not normal and thus, a non-

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